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(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM

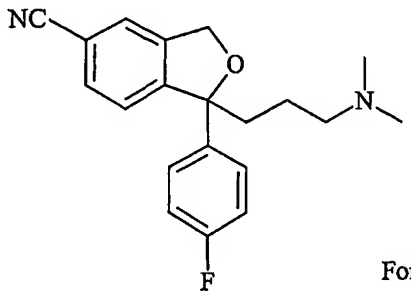
(57) Abstract: A method for the preparation of citalopram comprising reacting 5-carboxyphthalide successively with a Grignard reagent of 4-halo-fluorophenyl and a Grignard reagent of 3-halo-N,N-dimethyl-propylamine and then effecting ring closure of the resulting compound of Formula XI, to a compound of Formula IV, followed by conversion of the compound of Formula IV into citalopram is disclosed. Methods for the manufacture and conversion of the compound of Formula IV are also disclosed.

Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, methods for the preparation of intermediates used in the preparation of citalopram, and methods for conversion of said intermediates into citalopram.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



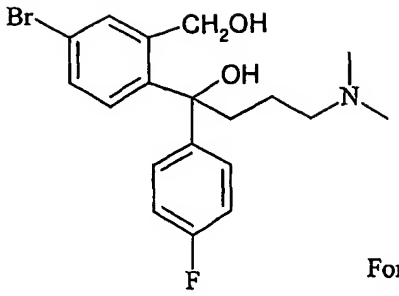
Formula I

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* **1982,** *6*, 277-295 and A. Gravem *Acta Psychiatr. Scand.* **1987,** *75*, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(*N,N*-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

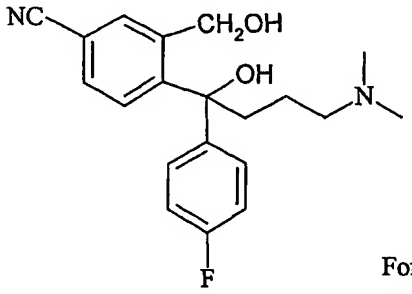
According to the method, which is only outlined in general terms, citalopram may be obtained by ring closure of the compound:



Formula II

in the presence of a dehydrating agent and subsequent exchange of the 5-bromo group with cuprous cyanide. The starting material of Formula II is obtained from 5-bromophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium chloride and *N,N*-dimethylaminopropyl magnesium chloride, respectively.

A new and surprising method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884, according to which an intermediate of the Formula



Formula III

is subjected to a ring closure reaction by dehydration with strong sulfuric acid in order to obtain citalopram. The intermediate of Formula III was prepared from 5-cyanophthalide by two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and *N,N*-dimethylaminopropyl magnesium halogenide, respectively.

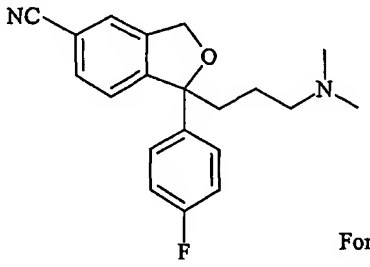
Further processes are disclosed in international patent application Nos. WO 98019511, WO 98019512 and WO 98019513. WO 98019512 and WO 98019513 relate to methods wherein a 5-amino-, 5-alkoxycarbonyl- or 5-(sec. aminocarbonyl)phthalide is subjected to two successive Grignard reactions, ring closure and conversion of the resulting 1,3-dihydroisobenzofuran derivative to the corresponding 5-cyano compound, i.e. citalopram. International patent application No. WO 98019511 discloses a process for the manufacture of citalopram wherein a (4-substituted-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure and the resulting 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran converted to the corresponding 5-cyano derivative,which is alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

Finally, methods of preparing the individual enantiomers of citalopram are disclosed in US Patent No 4,943,590 from which it also appears that the ring closure of the intermediate of Formula **III** may be carried out via a labile ester with a base.

It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable and safe procedure using convenient starting materials.

Summary of the invention

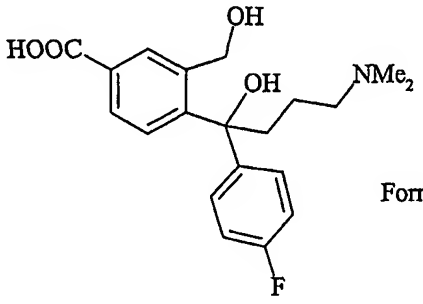
Accordingly, the present invention relates to a novel method for the preparation of citalopram having the Formula **I**



Formula I

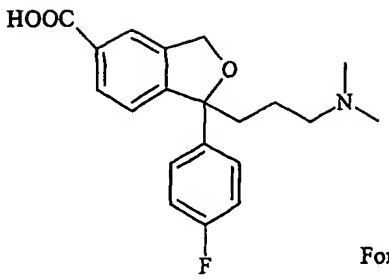
comprising:

reacting 5-carboxyphthalide successively with a Grignard reagent of 4-halo-fluorophenyl and a Grignard reagent of 3-halo-*N,N*-dimethyl-propylamine and then effecting ring closure of the resulting compound of Formula **XI**



Formula XI

to a compound of Formula **IV**



Formula IV

followed by conversion of the compound of Formula **IV**

into citalopram.

In particular, the invention relates to such a method comprising:

i) reaction of the compound of Formula **IV** with a dehydrating agent and a sulfonamide of the Formula H_2N-SO_2-R wherein R is:

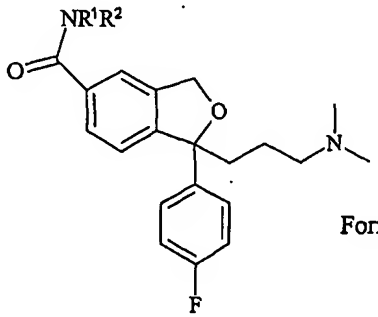
a) An optionally substituted NH_2, or C_{1-6} alkyloxy,

b) aryloxy or heteroaryloxy optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino, or

c) aryl or heteroaryl optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino ;

or

ii) conversion of the compound of Formula **IV** to the corresponding amide of Formula **V**

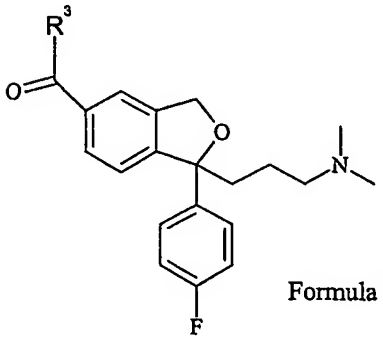


Formula V

in which R^1 and R^2 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more substituents selected from the group comprising aryl and heteroaryl, hydroxy, C_{1-6}-alkoxy, aryloxy, heteroaryloxy, aryl-C_{1-6}-alkoxy, or trisubstituted silyl wherein the substituents are independently C_{1-6} alkyl, aryl, heteroaryl or aryl-C_{1-6}-alkyl and then reacting the amide of Formula **V** with a dehydrating agent

thereby obtaining citalopram as the base or a pharmaceutically acceptable salt thereof.

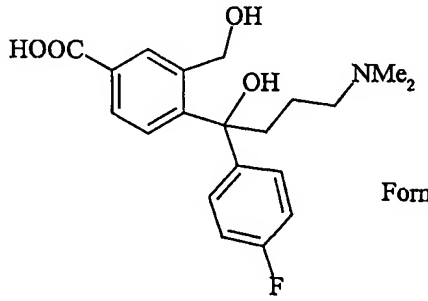
The conversion of the 5-carboxy derivative of Formula **IV** to the amide of Formula **V** may be carried out via an activated acid derivative of Formula **VI**:



Formula **VI**

wherein R^3 is halogen, C_{1-6} alkoxy, aryloxy, heteroaryloxy, aryl-C_{1-6}-alkoxy, heteroaryl-C_{1-6}-alkoxy, alkylcarbonate, arylcarbonate, alkylcarbamate, arylcarbamate, alkylthiocarbonate, arylthiocarbonate, alkylthiocarbamate, arylthiocarbamate, alkylacyloxy, arylacyloxy, heteroarylacyloxy substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

In another aspect, the invention relates to methods for the preparation of the intermediate of Formula **IV** comprising reaction of 5-carboxyphthalide successively with a Grignard reagent of 4-halo-fluorophenyl and a Grignard reagent of 3-halo-*N,N*-dimethyl-propylamine and then effecting ring closure of the resulting compound of Formula **XI**



Formula **XI**

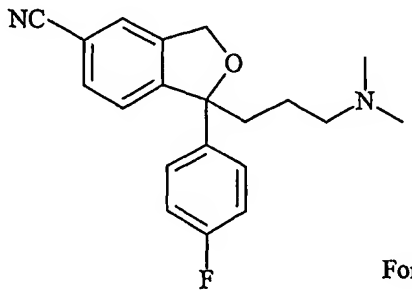
to a compound of Formula **IV**

The Grignard reagent of 4-halogen-fluorophenyl is a magnesium halide, such as the chloride, bromide or iodide. Preferably the magnesium bromide is used. The Grignard reagent of 3-halogen-*N,N*-dimethylpropylamine is a magnesium halide, such as the chloride, bromide or iodide, preferably the magnesium chloride. Preferably, the two reactions are performed successively without isolation of the intermediate resulting from the first Grignard reaction.

The ring closure of the compound of Formula **XI** is effected by an acid or via a labile ester with or without a base. Acidic ring closure is performed by an inorganic acid, such as a sulfuric or phosphoric acid, or an organic acid, such as methylsulfonic, p-toluenesulfonic or trifluoroacetic acid. The basic ring closure is performed via a labile ester, such as the methane sulfonyl, p-toluene sulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl ester with addition of a base, such as triethyl amine, dimethylaniline, pyridine, etc. The reaction is performed in an inert solvent, preferably with cooling, in particular about 0 °C, and is preferably carried out by a one-pot procedure, i.e. with esterification and simultaneous addition of the base.

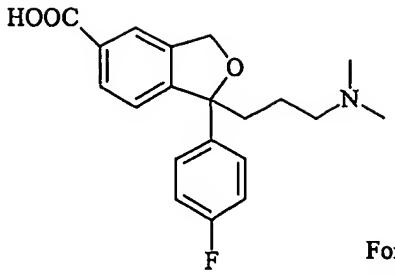
The 5-carboxyphthalide used as a starting material may be obtained by the methods described in US patent No. 3,607,884 or German patent No. 2630927, i.e. by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO_3 or by electrochemical hydrogenation of trimellithic acid.

In yet another aspect, the invention relates to a method for the preparation of citalopram



Formula I

comprising reacting a compound of Formula **IV**



Formula IV

with a dehydrating agent and a sulfonamide of the formula H_2N-SO_2-R wherein R is

a) An optionally substituted NH_2, or C_{1-6} alkyloxy,
b) aryloxy or heteroaryloxy optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino, or
c) aryl or heteroaryl optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino.

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram as the base or any convenient salt thereof manufactured by the process of the invention.

Throughout the specification and claims, the term 'dehydrating agent' refers to any suitable dehydrating agent and a person skilled in the art may easily determine the optimal agent. Examples of suitable dehydrating agents are $SOCl_2$, $POCl_3$, PCl_5, $SOBr_2$, $POBr_3$, PBr_5, SOI_2, POI_3, PI_5, P_4O_{10}, oxalylchloride, carbonyldiimidazole and Vilsmeier reagents. Preferably a chloro-containing agent, most preferably $SOCl_2$ or $POCl_3$, is used. Vilsmeier reagents are reagents formed by mixing of *N,N*-dimethylformamide (DMF) and dehydrating agents, examples of which are DMF/ $SOCl_2$ and DMF/ $POCl_3$.

Throughout the specification and claims, C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl. Similarly, C_{1-4} alkyl refers to such a group having from one to four carbon atoms inclusive and C_{1-6} alkoxy, C_{1-4} alkoxy and C_{1-4} alkylamine designate such groups wherein the alkyl moity is as defined.

Halogen means fluorine, chlorine, bromine or iodine.

In method i) of the invention, one possible but non-limiting mechanism of the reaction is that the 5-carboxy compound of Formula **IV** reacts with the dehydration agent in order to form a corresponding activated derivative, which then reacts with the sulfonamide, H_2N-SO_2-R,

thereby forming citalopram. During the latter reaction, a catalytic amount of an acid may be necessary.

The sulfonamide, H_2N-SO_2-R, used in the process is preferably sulfamide, NH_2-SO_2-NH_2.

The optionally substituted NH_2 used in the process is preferably *tert*-butylamine.

The reactions with dehydration agents in the method of the invention are carried out neat or in a suitable solvent, such as sulfolane or acetonitrile. When a solvent is used in the dehydration reaction of ii), a catalytic amount of *N,N*-dimethylformamide may be needed.

In one embodiment of the invention, the manufacture of the compound of Formula **IV** and the conversion of the compound of Formula **IV** into citalopram is performed without isolation of the compound of Formula **IV**, a so called 'one-pot synthesis'.

In another embodiment of the invention, the compound of Formula **IV** is at least partially isolated before conversion to citalopram.

The compound of Formula **I** may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as diethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting maschine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Examples

The invention is further illustrated by the following examples, which should not be construed as limiting the scope of the invention.

Example 1

5-Carboxy citalopram

To a stirred suspension/solution of 5-carboxyphthalide (1.0 g, 5.7 mmol) in dry THF (20 mL) under a nitrogen atmosphere was added *N,N,N',N'*-tetramethylethylenediamine (2.2 mL, 1.7 g, 14 mmol). A solution of *p*-fluorophenylmagnesium bromide (approx. 0.5 M) and magnesium bromide (approx. 0.125 M) in THF (approx. 60 mL) was added dropwise until no 5-carboxyphthalide remained. A solution of 3-(*N,N*-dimethylamino)propylmagnesium chloride in THF/heptane (approx. 2 M, approx 15 mL) was then added dropwise until none of the previous intermediate remained. The solution was then evaporated to give a crunchy solid. This solid was treated with saturated aqueous ammonium chloride solution (2 mL) and water (20 mL), and the pH was adjusted to pH 6 with aqueous hydrochloric acid solution (10

M). The solution was washed with ether. HPLC analysis of the aqueous layer indicated that the diol was present in sufficient purity to continue (> 90% purity, HPLC peak area – UV 220 nm). The pH was adjusted to pH < -1 with aqueous hydrochloric acid solution (10 M) and the solution was stirred for 2 h. HPLC analysis indicated that the 5-carboxy citalopram was present in sufficient purity for further use (> 80% purity, HPLC peak area – UV 220 nm).

Example 2

5-Cyano-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydro-isobenzofuran. (Citalopram, free base)

5-Carboxy-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydro-isobenzofuran (5 g, 0.015 mole) and sulfamide (1.65 g, 0.017 mole) were dissolved in sulfolane (15 mL). Thionylchloride (2.25 g, 0.019 mole) was added at room temperature and the temperature of the reaction mixture was raised to 130 °C for 2 hours. The reaction mixture was allowed to cool to 75 °C and water (25 mL) was added. The temperature was held at 75 °C for 15 min, and then the reaction mixture was cooled to room temperature. pH was ajusted to 9 with ammonium hydroxide and then n-heptane (75 mL) was added. The temperature was raised to 70 °C and the hot n-heptane layer was isolated, from which the title compound crystallised on cooling. Yield 3.77 g. Purity (HPLC peak area) > 97%.

Example 3

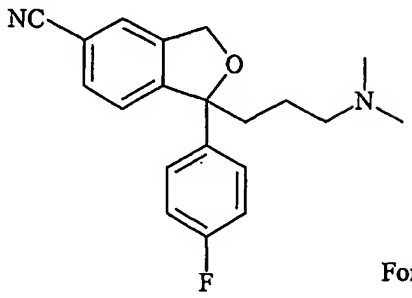
5-Cyano-1-(4-fluorophenyl)-1-(3-dimethylaminopropyl)-1,3-dihydro-isobenzofuran oxalate. (Citalopram, oxalate)

To a stirred solution/suspension of 5-carboxyphthalide (57 mmol) and *N,N,N',N'*-tetramethylethylenediamine (144 mmol) in THF (200 mL) was added a solution of *p*-fluorophenylmagnesium bromide (approx. 0.5 M) and magnesium bromide (approx 0.125 M) in THF dropwise until no more starting phthalide remained. A solution of 3-(*N,N*-dimethylamino)propylmagnesium chloride (approx. 2 M in THF/heptane) was added dropwise until no more of the previous intermediate remained. Methanesulfonyl chloride (228 mmol) was added dropwise over 5 minutes in an exothermic reaction. After 30 min, DMF (5 mL) was added, followed by $POCl_3$ (228 mmol) dropwise over 10 minutes in a mildly exothermic reaction and the mixture was stirred for 2h. *t*-Butylamine (285 mmol) was

added dropwise over 15 minutes and the mixture was stirred overnight. DMF (5 mL) was added dropwise, followed by $POCl_3$ (2.3 mol) over 1 h. The mixture was stirred overnight, and was then heated to reflux for 1 h. The mixture was cooled in and ice/water bath, and water (200 mL) was cautiously added dropwise over 1 h in an exothermic reaction. The mixture was basified to pH >9 with an aqueous solution of ammonia in water (25% w/v). Toluene (100 mL) was added, and the mixture was filtered. The residue was washed with further toluene, the combined filtrates were separated, and the organic phase was collected. The organic phase was extracted twice with an aqueous solution of H_2SO_4 (10 % v/v). The combined acid extracts were basified to pH >9 with an aqueous solution of ammonia in water (25% w/v) and were extracted with toluene. The combined toluene layers were dried and evaporated to give citalopram base as a dark oil. The oxalate salt was prepared using standard procedures to give citalopram oxalate. Yield 9.2 g. Purity (HPLC peak area) > 90%.

Patent Claims

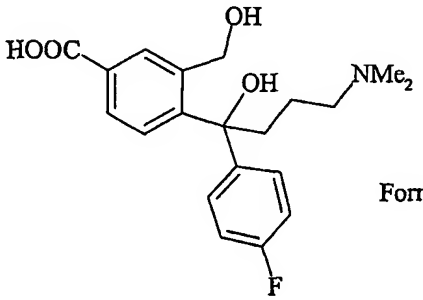
1. A method for the preparation of citalopram



Formula I

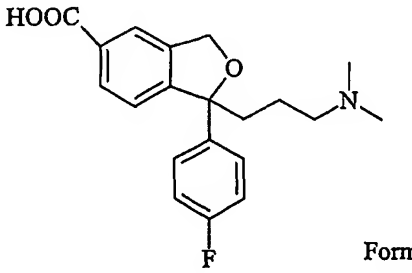
comprising

reacting 5-carboxyphthalide successively with a Grignard reagent of 4-halo-fluorophenyl and a Grignard reagent of 3-halo-*N,N*-dimethyl-propylamine and then effecting ring closure of the resulting compound of Formula **XI**



Formula XI

to a compound of Formula **IV**



Formula IV

followed by conversion of the compound of Formula **IV** into citalopram.

2. A method according to claim 1, characterised in that:

i) the compound of Formula **IV** is reacted with a dehydrating agent and a sulfonamide of the formula H_2N-SO_2-R wherein R is

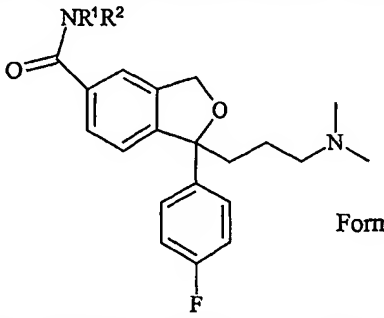
a) An optionally substituted NH_2, or C_{1-6} alkyloxy,

b) aryloxy or heteroaryloxy optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino, or

c) aryl or heteroaryl optionally substituted with halogen, C_{1-4}-alkyl, cyano, hydroxy, C_{1-4}-alkoxy, trifluoromethyl, nitro, amino, C_{1-4}-alkylamino or di-C_{1-4}-alkylamino;

or

ii) the compound of Formula **IV** is converted to the corresponding amide of Formula **V**



Formula **V**

in which R^1 and R^2 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more substituents selected from the group comprising aryl and heteroaryl, hydroxy, C_{1-6}-alkoxy, aryloxy, heteroaryloxy, aryl-C_{1-6}-alkoxy, or trisubstituted silyl wherein the substituents are independently C_{1-6} alkyl, aryl, heteroaryl or aryl-C_{1-6}-alkyl and then reacting the amide of Formula **V** with a dehydrating agent;

thereby obtaining citalopram as the base or a pharmaceutically acceptable salt thereof.

3. The method according to Claim 2, wherein the compound of Formula **IV** is reacted with $SOCl_2$ and sulfamide.

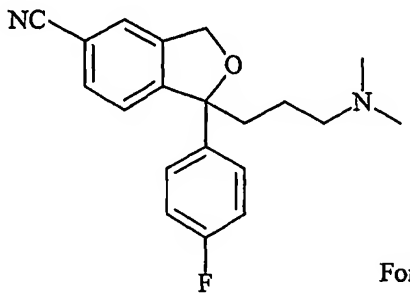
4. The method of Claim 3, characterised in that the reaction is performed in sulfolan.

5. The method according to Claim 2, wherein the compound of Formula **IV** is reacted with $POCl_3$ and *tert*-butylamine.

6. The method of claim 1, characterised in that the manufacture of the compound of Formula IV and the conversion of the compound of Formula IV is performed without isolation of the compound of Formula IV.

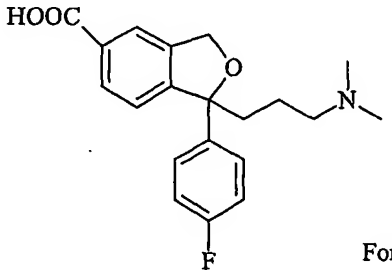
7. The method of claim 1, characterised in that the compound of Formula IV is at least partially isolated before conversion to citalopram.

8. A method for the preparation of citalopram



Formula I

comprising reacting a compound of Formula IV

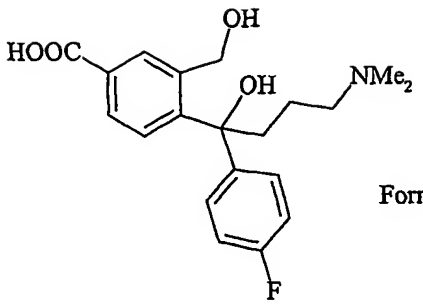


Formula IV

with a dehydrating agent and a sulfonamide of the formula $H_2N\text{-}SO_2\text{-}R$ wherein R is

d) An optionally substituted NH_2, or $C_{1\text{-}6}$ alkyloxy,
e) aryloxy or heteroaryloxy optionally substituted with halogen, $C_{1\text{-}4}$-alkyl, cyano, hydroxy, $C_{1\text{-}4}$-alkoxy, trifluoromethyl, nitro, amino, $C_{1\text{-}4}$-alkylamino or di-$C_{1\text{-}4}$-alkylamino, or
f) aryl or heteroaryl optionally substituted with halogen, $C_{1\text{-}4}$-alkyl, cyano, hydroxy, $C_{1\text{-}4}$-alkoxy, trifluoromethyl, nitro, amino, $C_{1\text{-}4}$-alkylamino or di-$C_{1\text{-}4}$-alkylamino.

9. A method for the preparation of a compound of Formula IV, characterised in that the compound of Formula IV is obtained by reaction of 5-carboxyphthalide successively with a Grignard reagent of 4-halo-fluorophenyl and a Grignard reagent of 3-halo-N,N-dimethyl-propylamine and then effecting ring closure of the resulting compound of Formula XI



Formula XI

10. Citalopram as the base or any convenient salt thereof manufactured by methods according to any of the claims 1-8.

11. A pharmaceutical composition comprising citalopram as the base or any convenient salt thereof according to claim 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00542

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	--	10-11
A	WO 0023431 A1 (H. LUNDBECK A/S), 27 April 2000 (27.04.00)	1-9
X	--	10-11
A	US 4136193 A (BØGESØ ET AL), 23 January 1979 (23.01.79)	1-9
X	--	10-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2001	27 -11- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/BS Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00542

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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